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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,761	03/13/2001	Parkash S. Gill	VASG-PO3-003	4201

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EXAMINER	
MCGARRY, SEAN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/805,761	GILL ET AL.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 June 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *18 June 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6.☒ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-4,8-11,14 and 19-21*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

SEAN McGARRY
PRIMARY EXAMINER
1635

Response to Arguments

Applicant's arguments filed 6/18/04 have been fully considered but they are not persuasive. Applicants arguments are addressed minus their reliance on the declaration of Parkash Gill, which is clearly directed to those grounds of arguments, presented in the first official Action of record and are not drawn solely to issues newly raised by the examiner in the final rejection. It does not appear that there were any new issues raised in the final rejection.

Applicant argues that the Uchida reference does not teach the specific sequence SEQ ID NO: 34 with the specific modifications of SEQ ID NO: 34 and the added limitation of new claims 19-21. Applicant argues that there is no motivation from Uchida et al or the other prior art references to make the invention as claimed. The examiners arguments of record are relied upon here since applicant's arguments are substantively the same as those presented throughout the prosecution of this application. A quick diagram of the target region and the antisense of Uchida in relation to the instant SEQ ID NO: 34 is provided to show the context of the examiner arguments. SEQ ID NO: 7 and 49-51 are from Uchida, SEQ ID NO: 49 and 50 provided 100% inhibition and SEQ ID NO: 51 provided 96% inhibition under the conditions of Uchida et al. SEQ ID NO:7 is shown in 3'-5' orientation.

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CCTACCGAACTTCTACATGAGCTAGAGTAGTCCCATGAGGAC  7
    UGGCTTGAAGATGTACTCGAU                   34
          AAGATGTACTCGATCTCATC               49
     GGCTTGAAGATGTACTGGAT                    50
CGGATGGCTTGAAGATGTA                         51
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It should be noted that SEQ ID NO: 50 of Uchida differs by only one nucleotide from SEQ D NO: 34 and that the specific region targeted by SEQ ID NO: 34 has been completely blanketed by antisense oligonucleotides that has great inhibitory capacity. Further, it is noted that none of this is new argument as these specific sequences have been pointed to repeatedly throughout the prosecution of the instant application. It is clear that one would have chosen this particular region to target for antisense compounds for use in inhibition of VEGF expression. The region is clearly shown to be an effective target and the instant inventions sequence differs by only one nucleotide from a specific sequence known in the art to be quite effective. That nucleotide not included in the specific sequence (of SEQ ID NO: 50) is included in another effective antisense oligonucleotide known in the art to be quite effective (SEQ ID NO: 51). Applicant has offered no reason or evidence to show any unexpected properties of the instantly claimed antisense oligonucleotide but only offers that maybe the antisense of the prior art will not work well in an in vivo environment if modified. No evidence to support this assertion is provided. Applicant argues that one would only modify antisense if they were intended to be used in cells. Well, the claims of Uchida et al are clearly drawn to methods of inhibition of VEGF *in vivo*. Clearly the antisense oligonucleotides are intended for cellular use. The Other prior art references relied upon all teach the use of antisense oligonucleotides as therapeutics, and further Robinson et al and Uchida et al specifically teach the use of Anisense oligonucleotides targeted to VEGF as therapeutics. Applicant argues that it would be unclear that 2'O-methyl-modifies oligonucleotides would be effective in cells unless there is evidence. Well,

again the prior art provides that such modifications (2'-O-methyl modifications) are used to provide enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. This point is important since applicant appears to believe, that since the use of phosphorothioate modified antisense in cells showed less inhibition than unmodified antisense in cell free assay indicates that one would not use such modifications in practice. This is a flawed argument. The modification provides protection from nucleases where they are present. If one uses non-modified antisense in cells they are more prone to nuclease degradation and thus is the very reason such modifications are used where nucleases are present. The environment of a cell is much more degradative to an antisense due to the presence of nucleases, for example. Applicant has attempted to use modifications and data that is associatively related and make it causatively related. Applicant has provided no evidence, such as a side by side comparison of the Uchida oligonucleotides (SEQ ID NOS: 549, 50 and 51, which are most closely related to SEQ ID NO: 34) in the targeted region, and shown that the oligos of the prior art would not function as the teachings of both the Agrawal and Bennett reference teach that they would with the same modification of SEQ ID NO: 34. Both the Agrawal and Bennett references have taught that it is beneficial in therapeutic antisense applications to use 2'-O-methyl modifications. Applicant should note that the specific Example 5 pointed to in Bennett et al is directed to those same 2'-O-methyl modifications claimed (including the newly added limitation of including a phosphorothioate linkage, for example). The disclosure of both of these references make it clear that one would chose such a modification (See columns 6-10 of Bennett et

al for example) for therapeutic applications, for example. The prior art, taken as a whole, clearly teaches the claimed invention.